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THROMBOSIS AND HEMOSTASIS

Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis

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KEY POINTS

- **Immediate compression therapy after DVT is associated with a 20% absolute reduction of RVO.**
- **The reduction of residual thrombosis is associated with an 8% absolute reduction of postthrombotic syndrome at 24 months.**

Thus far, the association between residual vein occlusion and immediate compression therapy and postthrombotic syndrome is undetermined. Therefore, we investigated whether compression therapy immediately after diagnosis of deep vein thrombosis affects the occurrence of residual vein obstruction (RVO), and whether the presence of RVO is associated with postthrombotic syndrome and recurrent venous thromboembolism. In a prespecified substudy within the IDEAL (individualized duration of elastic compression therapy against long-term duration of therapy for prevention of postthrombotic syndrome) deep vein thrombosis (DVT) study, 592 adult patients from 10 academic and nonacademic centers across The Netherlands, with objectively confirmed proximal DVT of the leg, received no compression or acute compression within 24 hours of diagnosis of DVT with either multilayer bandaging or compression hosiery (pressure, 35 mm Hg). Presence of RVO and recurrent venous thromboembolism was confirmed with compression ultrasonography and incidence of postthrombotic syndrome as a Villalta score of at least 5 at 6 and 24 months. The average time from diagnosis until assessment of RVO was 5.3 (standard deviation, 1.9) months. A significantly lower percentage of patients who did receive compression therapy immediately after DVT had RVO (46.3% vs 66.7%; odds ratio, 0.46; 95% confidence interval, 0.27-0.80; $P = .005$). Postthrombotic syndrome was less prevalent in patients without RVO (46.0% vs 54.0%; odds ratio, 0.65; 95% confidence interval, 0.46-0.92; $P = .013$). Recurrent venous thrombosis showed no significant association with RVO. Immediate compression should therefore be offered to all patients with acute DVT of the leg, irrespective of severity of complaints. This study was registered at ClinicalTrials.gov (NCT01429714) and the Dutch Trial registry in November 2010 (NTR2597). (*Blood*. 2018;132(21):2298-2304)

Introduction

Although most guidelines for the management of deep vein thrombosis (DVT) emphasize the pharmacological treatment with anticoagulants, and mainly focus on prevention of recurrent events, little attention is directed toward the prevention of long-term outcomes such as postthrombotic syndrome.[1-3]

Postthrombotic syndrome is the most frequent complication of DVT, affecting 20% to 50% of patients 1 to 2 years after DVT.[4-7] It is a chronic condition that is characterized by mild to severe symptoms and signs of venous insufficiency ranging from pain to sensation of leg heaviness, discomfort, pretibial edema, skin induration, and hyperpigmentation to venous ulceration in the most severe cases. The Villalta scale is a tool to diagnose and define the severity of postthrombotic syndrome, using the above-mentioned signs and symptoms.[8] Because of its frequency, possible severity, and chronicity, postthrombotic syndrome is not only costly but is also associated with a decrease in quality of life.[9-11] At this time, there is no cure for the condition; therefore, acute treatment of DVT should include prompt prevention of postthrombotic syndrome.

Postthrombotic syndrome is thought to be a result of venous hypertension, caused by a combination of vein-wall remodeling,

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residual vein obstruction (RVO), and valvular reflux.[12-16] The role of RVO as an independent risk factor for the onset of postthrombotic syndrome remains controversial. Known risk factors for postthrombotic syndrome are, among others, older age (relative risk [RR], 1.3-3),[5,17-19] obesity (RR > 2),[5,17,19,20] history of ipsilateral DVT (RR, 6-7),[18-22] proximal DVT (RR, 2-3),[22,23] preexisting primary venous insufficiency (RR, 1.2–1.8),[22] and inadequate international normalized ratio control during first 3 months of warfarin treatment (RR, 2.7).[21]

The role of compression for the prevention of postthrombotic syndrome is undecided. A recent guidance for prevention of postthrombotic syndrome solely recommends optimal anticoagulant treatment of DVT with the use of pharmacologic agents or mechanical thromboprophylaxis in high-risk patients.[24,25] Once venous thrombosis has occurred, there is a weak recommendation (class IIB) against routine use of elastic compression stockings to prevent postthrombotic syndrome. Nevertheless, a recent Cochrane meta-analysis showed that a 30% reduction in the occurrence of postthrombotic syndrome could be achieved by application of compression stockings.[24-26] Elastic compression stockings are usually prescribed and fitted once the acute edema has resolved. Until then, it is customary in The Netherlands to offer early compression therapy in the form of multilayer compression bandaging or compression hosiery starting within 24 hours after DVT. The immediate compression phase typically comprises 4 weeks after the acute event of thrombosis and ends as soon as the edema is resorbed and compression stockings are fitted. To date, little is known about the effect of immediate compression in this early stage of the thrombosis; only 3 small, randomized controlled trials (n = 45, n = 69, n = 73) have been published.[27-29] All these studies found an effect of direct compression therapy on occurrence of postthrombotic syndrome and recanalization in the short term. Moreover, 2 of them reported faster reduction of pain and swelling with compression. However, long-term effects were negative,[28] not assessed,[29] or uncertain.[27] Furthermore, the effect of compression on occurrence of RVO, and the role of RVO in relation to risk for recurrence, is not unequivocally clear.[30]

The aim of the current study is to investigate the effect of immediate compression therapy on the presence of RVO, and to assess the association of RVO with the incidence of postthrombotic syndrome 6 and 24 months after venous thrombosis, as well as the association between RVO and recurrent venous thromboembolism within 24 months.

Methods

For this study, no separate ethical approval was needed or acquired, but data from the IDEAL (individualized duration of elastic compression therapy against long-term duration of therapy for prevention of postthrombotic syndrome) study were used. For the IDEAL study, ethical approval was obtained by the institutional review board of Maastricht University Medical Centre and acknowledged by the ethical review boards of participating centers (NL 32073.068.10). The trial was funded by a grant by ZonMw The Netherlands (grant number 171102007). The trial was registered at ClinicalTrials.gov (NCT01429714). All participants gave written informed consent before any study-related activity was performed.

Study design and population

The present study is a prespecified substudy of the IDEAL DVT study.

Briefly, the IDEAL DVT study was a randomized controlled noninferiority trial that included 865 adult patients with objectively confirmed proximal DVT, without any history of previous ipsilateral venous thrombosis and without signs of venous insufficiency in 12 centers in The Netherlands and 2 centers in Italy. The study compared fixed duration of elastic compression therapy with tailored duration based on clinical signs and symptoms (the Villalta score). The study has been described in detail previously.[31] The current substudy assessed the presence of RVO at 1 week before cessation of anticoagulant treatment. Ten of the 12 Dutch centers that participated in the IDEAL DVT trial also participated in the present study; the 2 Italian centers did not participate.

In the acute phase, compression was initiated and executed according to 3 prespecified protocols, 1 per participating center. One center followed the protocol of no initial compression, 7 centers applied short stretch multilayer compression bandaging (thigh high with 30-40 mm Hg pressures applied), and 2 centers used compression hosiery (Mediven Struva 35 mm Hg) initially until edema was resorbed and compression stockings were fitted. After this initial phase, all patients wore fitted compression stockings for 6 months. All patients participating in the RVO substudy were anticoagulated for a period of at least 3 months. The mean time within therapeutic range for the first 3 months of treatment of the patients anticoagulated with vitamin K antagonists within the 10 study sites that participated in the substudy was provided by the anticoagulation clinics and calculated according to the Rosendaal method.[32]

The current study assessed the presence of RVO at 1 week before cessation of anticoagulant treatment. Ten of the 12 Dutch centers participated in the present substudy; the 2 Italian centers did not participate.

The outcomes

When discontinuation of anticoagulation was considered, independent radiologists in the participating centers performed compression ultrasonography to determine the presence of RVO, guided by a prespecified protocol based on literature.[33] The patients were in a supine position, and the examined vein was imaged in a transverse plane. RVO was defined as the persistence of thrombotic material resulting in a diameter of at least 2 mm during full compression in either the common femoral vein at the groin or the popliteal vein in the popliteal fossa. The radiologists were required to describe the findings systematically according to 1 standard, provided by the study. Technical devices were dependent on the hospital's preferences and availability. Postthrombotic syndrome was assessed using the International Society on Thrombosis and Haemostasis consensus scoring method: a total Villalta score of at least 5 at least 6 months after the diagnosis of DVT. An independent radiologist objectively confirmed the occurrence of recurrent venous thromboembolism.

Statistical analysis

Baseline differences between the groups with and without compression in the acute phase were assessed on the basis of the χ^2 test for categorical variables, and 1-way analysis of variance for continuous variables. The presence of RVO was analyzed as a binominal outcome. For the associations among RVO, compression in the acute phase of DVT, and recurrent venous thromboembolism, multivariate logistic regression was performed. Analyses were adjusted for statistically significant

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baseline differences: extent and type of thrombosis (provoked, unprovoked). Analyses were also adjusted for treatment effect after 6 months (individualized or standard duration of elastic compression stockings, the IDEAL intervention effect). Sensitivity analysis was performed with complete cases and by performing the analyses restricted to the group of patients with DVT in the common femoral vein. The level of statistical significance was set at a P value of ≤.05. The software program SPSS version 23.0 was used for all analyses.

Results

In total, 592 patients with a mean age of 57.0 years (standard deviation [SD], 15.0 years) participated in this study. The majority (57.8%) were men. The average body mass index was 28.2 kg/m^2 (SD, 5.3 kg/m^2). A history of contralateral DVT was seen in 10.1%. In 52.2% of patients, the DVT was located in the popliteal vein, followed by the femoral vein in 27.5% and the common femoral vein in 20.1%. The left leg was involved in 52.7% and the right leg in 46.5%, and 0.8% of patients had bilateral DVT. The majority of patients (80.6%) were prescribed vitamin K antagonists, 3.0% received direct oral anticoagulants, 11.1% used investigational anticoagulants (either warfarin or rivaroxaban), and 4.4% used low-molecular-weight heparin monotherapy. The mean duration of anticoagulant therapy was 258 (SD, 178) days. The meantime within therapeutic range for short-term anticoagulation therapy (first 3 months of treatment) was 74.03% (SD, 3.7%) for the sites with immediate compression (both multilayer bandaging and compression hosiery) and 76.07% (SD, 4.6%) for the site without initial compression. The average time from diagnosis to the assessment of RVO was 5.3 (SD, 1.9) months. Table 1 provides the baseline characteristics of the study population for clinical characteristics.

Overall, in the acute phase, 72 patients (12.2%) received no compression, multilayer compression bandaging was applied in 369 patients (62.3%), and compression hosiery was applied in 151 patients (25.5%). Statistically significant differences in the compression groups were observed with regard to thrombus location and type of DVT. In the noncompression group, thrombus location was at the level of the popliteal vein in 39.4%, in 28.2% femoral, and in 32.4% common femoral. For the compression group, this was 54.0% (range across centers, 43.9%-65.0%), 27.5% (range across centers, 0%-43.9%), and 18.5% (range across centers, 5.9%-45.5%), respectively (P = .014). Provoked DVT was observed in 42.3% of the patients without compression and 29.3% (range across groups, 13.3%-48.5%) of the patients with compression therapy (P = .046).

Compression in the acute phase and RVO

In total, 289 (48.8%) of 592 patients had RVO on ultrasound (Table 2). Of the patients in the noncompression group, 66.7% had RVO compared with 46.3% of the patients who received compression therapy (47.4% for compression bandaging, 43.7% hosiery). This corresponds to an absolute reduction of 20.4% (OR, 0.46; 95% CI, 0.27-0.80; P = .005) of RVO when compression therapy is applied in the acute phase.

RVO and postthrombotic syndrome

Table 3 illustrates the occurrence of RVO in relation to postthrombotic syndrome at 6 and 24 months after DVT, and recurrent venous thromboembolism at 24 months after DVT. At 6 months, 55.7% of patients with RVO had postthrombotic syndrome compared with 44.3% without RVO (OR, 0.66; 95% CI, 0.46-0.96; P = .029). The same trend was observed at 24 months: patients without RVO less often had postthrombotic syndrome (46.0%) than patients with RVO (54.0%; OR, 0.65; 95% CI, 0.46-0.92; P = .013). Subgroup analyses with only patients who were diagnosed with DVT in the common femoral vein showed no significant effect of immediate compression in the acute phase on presence of RVO. RVO was observed in 65.2% of the patients with common femoral vein thrombosis in the no compression group, and in 64.6% of the patients with compression (OR, 0.93; 95% CI, 0.35-2.43; P = .579). RVO was also not significantly associated with postthrombotic syndrome at 24 months (OR, 0.77; 95% CI, 0.54-1.12, P = .186) in this subgroup of patients.

Table 1. Baseline demographic and clinical characteristics (N = 592)

Characteristics	
Mean age, y (SD)	57.0 (15.0)
Male, N (%)	342 (57.8)
Mean body mass index, kg/m^2 (SD)	28.2 (5.3)
Previous DVT contralateral, N (%)	70 (10.1)
Provoked thrombosis, N (%)	182 (30.7)
DVT location, N (%)	
Popliteal vein	309 (52.2)
Femoral vein	163 (27.5)
Common femoral vein	119 (20.1)
Left leg	312 (52.7)
Right leg	275 (46.5)
Bilateral	5 (0.8)
DVT treatment (%)	
Vitamin K antagonist*	477 (80.6)
Nonvitamin K anticoagulants†	18 (3.0)
Investigational anticoagulants‡	61 (11.1)
Low molecular weight heparin	26 (4.4)
Duration anticoagulant therapy (days)	258 (178)
Average time from diagnosis to second ultrasound, months (SD)	5.3 (1.9)
Compression therapy in the acute phase of DVT (%)	
No initial compression	72 (12.2)
Initial compression therapy	520 (87.8)
Multilayer compression bandaging	369 (62.3)
Compression hosiery	151 (25.5)

*All patients with vitamin K antagonist had initially 5 to 10 days of low molecular weight heparin.

†The only direct oral anticoagulants used during the study was rivaroxaban.

‡Some patients participated in studies comparing investigational anticoagulants (warfarin vs edoxaban), low molecular weight heparin in patients with malignancy.

RVO and recurrent thromboembolism

No significant association between RVO and recurrent venous thromboembolism was observed (Table 3). A total of 30 recurrent events of DVT were observed, during the study of which 60% had RVO compared with 40% without RVO (OR, 0.82; 95% CI,

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Table 2. Residual vein occlusion in relation to compression in the acute phase after DVT

	Compression								No compression		
	Compression			Multilayer compression			Compression hosiery				
	N	%	OR (95%CI)	N	%	OR (95%CI)	N	%	OR (95%CI)	N	%	OR (95%CI)
RVO	241/520	46.3	0.46 (0.27-0.80)	175/369	47.4	0.48 (0.27-0.84)	66/151	43.7	0.42 (0.23-0.78)	48/72	66.7	—
No residual vein obstruction	279/520	53.7	—	194/369	52.6	—	85/151	56.3	—	24/72	33.3	—

DVT analysis adjusted for thrombus location, type of DVT, and history of DVT. No compression was used as the reference group for all analyses.
CI, confidence interval; OR, odds ratio.

0.61-2.12; $P = .263$). Recurrent pulmonary embolism occurred in 19 patients in total, of whom 52.6% had RVO and 47.7% did not (OR, 0.95; 95% CI, 0.61-1.46; $P = .805$).

Discussion

This study shows that starting compression treatment in the acute phase, as soon as 24 hours after the diagnosis of DVT, significantly reduces the absolute incidence of RVO with 20.4%. Moreover, the incidence of postthrombotic syndrome both at 6 and at 24 months was significantly lower in patients without RVO compared with patients with RVO, with an absolute difference of 11.4% at 6 months and 8% at 24 months. This suggests that RVO does contribute to the development of postthrombotic syndrome, and that compression therapy may prevent postthrombotic syndrome from the very early start of thrombosis treatment. The efficacy of both multilayer bandaging compression and compression hosiery was similar. Our data do not show a significant association of RVO with the occurrence of recurrent venous thromboembolism; the number of recurrences was, however, too low to allow for a definitive conclusion.

Our study has some weaknesses; first, this is a subanalysis of data from a large randomized trial, and the study sample as such is not randomized. However, adjustments for differences in distribution of patient characteristics between the groups were made in the analyses. Furthermore, a small proportion of patients were anticoagulated with a direct oral anticoagulant or low-molecular-weight monotherapy. It has been suggested that these types of anticoagulation may influence the risk for postthrombotic syndrome. Another potential weakness is the fact that only assumptions can be made on the mode of action of compression; therefore, the data do not allow inference for causality. There are, however, several strengths. First, this is the first study with a long-term follow-up of patients and with a sufficiently large sample size to provide reliable information on the clinical importance of early compression therapy after acute DVT. Second, the assessor-blinded design that included frequent assessments of the leg provided sufficient and dependable data for analysis.

Only 3 studies have been performed on the efficacy of early compression therapy in the acute phase so far. One trial (n = 45) randomly assigned patients to inelastic bandages plus walking exercises, elastic compression stockings plus walking exercises, or no compression with bed rest.[27] After 2 years, less postthrombotic syndrome was seen in patients randomly assigned to compression therapy and ambulation[34]; it is uncertain whether this was the effect of early compression or walking exercises. Roumen-Klappe et al randomly assigned patients between immediate multilayer compression bandages and no compression before application of elastic compression stockings.[28] This study (n = 69) found a reduction of symptoms and edema in the first week, but no difference in postthrombotic syndrome after 1 year. The third trial (n = 73) compared acute initiation of compression hosiery with hosiery starting after 14 days.[29] Better recanalization of the thrombus was detected at 14 and 90 days in patients in whom acute initiation of hosiery was applied, but long-term effects on postthrombotic syndrome were not assessed. Hence, our study fills both the need for a larger sample size and the evaluation of long-term effects.

In the last decade, improvements have been achieved mainly in the pharmacological treatment of DVT, in terms of reducing

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Table 3. Residual vein occlusion in relation to postthrombotic syndrome and recurrent venous thromboembolism

	No residual vein obstruction		Residual vein obstruction		
	N	%	N	%	OR (95%CI)
Postthrombotic syndrome at 6 and 24 mo after DVT*					
Villalta score ≥5 at 6 mo	77/174	44.3	97/174	55.7	0.66 (0.46-0.96)
Villalta score ≥5 between at 24 mo	142/309	46.0	167/309	54.0	0.65 (0.46-0.92)
Recurrent venous thromboembolism between 6 to 24 mo*					
DVT	12/30	40.0	18/30	60.0	0.82 (0.61-2.12)
Pulmonary embolism	9/19	47.7	10/19	52.6	0.95 (0.61-1.46)

Analyses adjusted for the intervention effect in IDEAL DVT study.

the risk for recurrence against a lower risk of bleeding. However, to date, no effective therapy in the acute phase is available to help restore venous patency and reduce the risk for long-term sequelae such as postthrombotic syndrome.

Our conclusion suggests that early compression treatment results in a lower incidence of residual vein thrombosis, and consequently in less postthrombotic syndrome, and is in line with expectations based on the open vein hypothesis: "early thrombus resolution results in less postthrombotic syndrome because there is less vein wall damage due to the shorter duration that the thrombus is adjacent to the vessel wall."

The use of early catheter-directed thrombolysis to restore venous patency was expected to effectively reduce the risk for postthrombotic syndrome in selected patients with more proximal extended thrombosis. However, so far, thrombolysis has been consistently associated with an increased risk of bleeding, but its effectiveness has not been unequivocally proven.[34,35]

Compression therapy has virtually no contraindications and harbors no risk of bleeding. In our population, 119 patients (20.1%) were diagnosed with a proximal DVT in the common femoral vein. We found that especially in this subset of patients, early compression therapy might not be effective, highlighting the importance of correct identification of patients eligible for treatment strategies in the acute phase, and the need for additional treatment options.

How precisely immediate compression therapy affects the recovery of venous patency cannot be answered by the current study. We may only hypothesize that mechanical compression reduces the vein diameter, and thereby increases the venous return, and as a result, promotes thrombus resolution.[36,37] Better venous return reduces edema and improves calf muscle function.[38] Moreover, compression therapy restores the microcirculation, thereby promoting the inflammatory response necessary for thrombus resolution. Current guidelines suggest application of compression only in cases where patients experience symptoms.[1] In alignment with this, some clinicians only tend to apply immediate compression therapy if the patient presents with more severe symptoms of DVT. The results of our study indicate, however, that immediate compression therapy not only should be applied in patients with increased symptomatology merely to reduce symptoms but also, more important, should be applied in all patients, even in those who are asymptomatic, to prevent postthrombotic syndrome. That impaired thrombus resolution is an important driver in the onset of postthrombotic syndrome is also known from earlier studies showing that subtherapeutic anticoagulant therapy, and thereby insufficient inhibition of the formation of thrombin and activation of thrombin activatable fibrinolysis inhibitor, is a risk factor for postthrombotic syndrome.[21,39] Subtherapeutic international normalized ratio was found to increase the risk for postthrombotic syndrome almost 2-fold, whereas adequate anticoagulation therapy reduced the risk for postthrombotic syndrome by 11.9%[40] A risk reduction of the same order was found among patients using direct oral anticoagulants compared with warfarin, but this was not statistically significant and needs further corroboration.[41] Also, long-term treatment with low-molecular-weight heparin in comparison with warfarin treatment has been shown to result in lower incidences of postthrombotic syndrome.[42] The effect of immediate compression therapy is similar to the effect of improvement of anticoagulant therapy. In our sample, the time within therapeutic range was found to be adequate and highly comparable between centers with and without immediate compression therapy.

We suggest, therefore, that compression therapy should be added to new pharmacological strategies to achieve optimal prevention of postthrombotic syndrome. The application of immediate compression therapy within 24 hours of the diagnosis of DVT is common clinical practice in most Dutch hospitals. It is therefore shown that it is feasible to provide such care.

The cost-effectiveness of the application of immediate compression for all patients with acute DVT should be investigated. It may be anticipated that the application of multilayer bandaging will be less cost-effective compared with compression hosiery. Furthermore, patients with iliofemoral DVT did not profit from immediate compression to the same extent as patients with less extensive DVT. Future research should be directed at better understanding of the underlying pathophysiology, and should be tailored to the individual patient's needs. The use of prediction models might assist physicians in the allocation of adjunctive treatment modalities to those who are likely to profit most.

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In conclusion, we suggest that in addition to adequate anticoagulation therapy, immediate compression therapy (either with multilayer bandaging or with compression hosiery) should be implemented in daily clinical practice, and that the application of early compression therapy in patients with acute DVT should be irrespective of symptomatology to optimize the prevention of postthrombotic syndrome. Furthermore, identification of patients at increased risk for postthrombotic syndrome should be performed in the acute phase to be able to provide these patients with adjunctive treatment.

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Authorship

Contribution: All authors designed the study; E.E.A. and A.J.t.C.-H. analyzed the data; E.E.A., I.M.B., M.t.W., and A.J.t.C.-H. wrote the manuscript; and all authors included patients and collected the data, were involved in the study, and critically reviewed and approved the final manuscript.

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Footnotes

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